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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,359	01/31/2002	Scot R. Weinberger	CiphBio-9	5296
1473	7590	08/25/2005	EXAMINER	
FISH & NEAVE IP GROUP ROPES & GRAY LLP 1251 AVENUE OF THE AMERICAS FL C3 NEW YORK, NY 10020-1105			DAVIS, DEBORAH A	
			ART UNIT	PAPER NUMBER
			1641	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/066,359

Applicant(s)

WEINBERGER ET AL.

Examiner

Deborah A. Davis

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 6,9-14,27 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 6,9-14,27 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

5.22

DETAILED ACTION

1. Applicants' response to the Office Action mailed on November 2, 2004 has been acknowledged. Currently, claims 6, 9-14 are pending; which includes newly added claims 27-28. Claim 7 has been cancelled.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
2. Claims 6, 9-14 and 27-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
3. Claim 6, step (a) recites "adsorbing separately a subset of proteins from each of the two complex biologic samples" is confusing because it appears to be only one subset of proteins being adsorb. The examiner suggestion is "adsorbing separately two subsets of proteins, one from each of the two complex biologic samples" would be clear.
4. Claims 27 recites "the amino acid sequence" in lines 4 and 8 lack antecedent basis.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1641

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 6, 9-14 and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over William T. Hutchens (WO98/59362) in view of Yates et al (USP#6,017,693).

The instant claims are directed to a method for identifying a protein that is differentially displayed between two complex biologic samples using mass spectrometry. William T. Hutchens teaches methods for identifying analytes that are differentially expressed between biological materials using desorption spectrometry which is the first mass of the uncleaved proteins as described in steps (a) through (b) (see abstract). The two samples are differentially displayed because the proteins can be expressed in different cell types being normal versus pathologic cancer cells. The method may indicate that a protein or other biomolecule is increased or decreased in expression, or is changed in some way based on different mass (page 63, lines 1-32). Hutchens teaches applicant's step (c) through (d) by teaching the fragmenting of large proteins into smaller pieces by enzymatic digestion increases sensitivity in detection of protein fragments. Fragmentation can be achieved by any means known in the art; some examples are enzymes such as glycosidase, endoproteases (page 64, lines 28-32). William T. Hutchens teaches proteins that are differentially present in two samples will increase the number of signals from that protein (page 64, lines 11-24). William T. Hutchens teaches that these methods of protein identification are useful for identifying diagnostic markers of disease expressed in a patient sample or a diseased cultured cell

Art Unit: 1641

compared to normal samples (page 64, lines 1-10). Maps of the protein samples are compared, which may indicate increased or decreased expression in a protein (page 63, lines 22-32). Accordingly, the matched parameters can be set to identify the closeness-of-fit between the protein analyte characteristics and the characteristics of the reference polypeptides in the database (page 61, lines 15-31). William T. Hutchens' method further includes a capture probe to capture proteins. William T. Hutchens' instant reference teaches probes for the specific detection of one or more analytes by desorption spectrometry, which can be prepared by selecting markers (candidates) to be detected (page 59, lines 19-33). The reference of Hutchens teaches the use of a Retentate chromatography to separate multiple analytes in parallel (page 52, lines 27-33).

The reference of Hutchens does not teach detection of the cleavage products with tandem mass spectrometry and utilizing its information for correlation as describe in steps (e) through (g).

However, the reference of Yates et al teaches applicant's correlation steps utilizing tandem mass spectrometry. Yates teaches that known amino acid sequences in a protein sequence library are used to calculated or predict one or more candidate fragment spectra. The predicted fragment spectra are then compared with an experimentally-derived fragment spectrum to determine the best match of the parent peptide. The result will be a plurality of candidate peptides, each with a predicted fragment spectrum. The predicted fragment spectra can then be compared with the fragment spectrum derived from the tandem mass spectrometer to identify one or more

proteins (column 2, lines 5-27). Correlating peptides analyzed by tandem mass spectrometer has an amino acid sequence identical to a sequence taken from the protein sequence library, which resulted in a predicted mass spectrum of an experimentally-derived fragment spectrum. When the peptide is analyzed by tandem mass spectrometer was derived from the protein, it is believed that the parent protein is identical to the protein whose sequence can be identified by a sequence library (column 4, lines 9-30). The examiner interprets the teaching of Yates as the second mass taken of the peptide fragments to identify the sequence information thereby identifying a candidate protein as described in step (g). The sequence of the candidate protein, which involves the mass information of the sequence can then be correlated to the first mass spectra of the parent protein as recited in step (b) so as to determine the differentially displayed protein as the candidate.

Therefore it would have been obvious to one of ordinary skill in the art to include in the teachings of Hutchens tandem mass spectrometry that yields sequence information of the fragment spectrum as taught by Yates et al to enable identification of the original parent protein. One of ordinary skill would be motivated because candidate sequences can be identified with high accuracy.

Response to Arguments

7. Applicant argues that the reference of Hutchens does not disclose any method of correlating information obtained from the differential presence of a protein in an analyte with information obtained from fragmenting that protein in order to identify the

Art Unit: 1641

differentially displayed protein. Applicant further argues that the reference of Dongre did not suggest performing MS-MS on fragments of proteins shown to be differentially present in a sample by prior mass spectrometry, and therefore there is no suggestion in Dongre to combine those methods. Applicant further asserts that even if there were motivation to combine, both references still lack the correlation step (g) of amended claim 6 because there is no teaching to determine the predicted masses of those "protein sources" or to correlate those predicted masses with the mass of a differentially expressed protein that was detected in the samples before protein cleavage.

Applicant's arguments have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Yates et al above that teach applicant's correlation step (g).

8. Applicant argues that the reference of Liebler does not teach steps (a) and (b) of amended claim 6, that include determining the mass of differentially displayed proteins with LDI mass spectra. Applicant argues that Liebler's method starts with enzymatic digestion of two samples followed by detection and selection of peptides. Applicant further asserts that Liebler alone or in combination with Dongre provide no teaching or suggestion that any masses of uncleaved proteins are ever determined by LDI mass spectrometry. ***Applicant's arguments have been fully considered and are persuasive. The rejection of Liebler in view of Dongre has been withdrawn.***

Conclusion

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

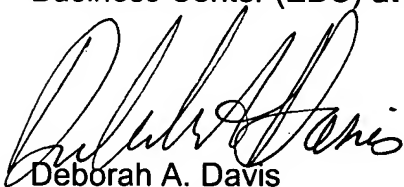
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A. Davis whose telephone number is (571) 272-0818. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1641

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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July 26, 2005



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08/03/05